UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/982,284	12/01/1997	HENRYK LUBON	030523/0141	9099

7590 01/08/2002

FOLEY & LARDNER
3000 K Street Suite 500
Washington, DC 20007-5109

EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1633	31

DATE MAILED: 01/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/982,284	LUBON ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's arguments and declaration by Dr. Serguei Soukharev filed 11-5-01, paper number 30, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74 have been canceled. Claims 75-100 have been added. Claims 75-100 are pending and under consideration in the instant application.

Claim Objections

"...an uromodulin" should be "a uromodulin" (claims 75, 80, 83, 88, 93, 96).

"...an urinary kallikrein" should be "a urinary kallikrein" (claims 75, 80, 83, 88, 93, 96).

"...an urinary thrombomodulin" should be "a urinary thrombomodulin" (claims 75, 80, 83, 88, 93, 96).

"...an uropontin" should be "a uropontin" (claims 75, 80, 83, 88, 93, 96).

There should be a comma after "nephrocalcin gene" in claims 75, 80, 83, 88, 93, 96.

There should be a comma after "bone morphogenetic protein" in claims 86 and 99.

Claim Rejections - 35 USC § 112

1. Claims 75-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants argue the specification discloses using the 5' regulatory sequences listed in claim 75 and 88 which are isolated from genes known to be associated with urinary tract tissue (page 20-27). Therefore, applicants argue the specification provides adequate written description of the 5' regulatory sequences claimed. Applicants argument is not persuasive. 1) While Simonet of record (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught using the apolipoprotein E promoter to obtain expression of a protein in the kidney of transgenic mice (p 28, line 3), Simonet did not teach the mice secreted the protein in their urine. 2) The specification and art did not teach the nucleic acid sequence of the uromodulin, renin, erythropoietin, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin promoter. 3) The specification does not teach an assay to determine the promoters of the uromodulin, renin, erythropoietin, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin gene. 4) The specification and the art did not teach there were more than one uromodulin, renin, erythropoietin, apolipoprotein E, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin gene. I.e. "a" uromodulin gene lacks written description because any and all uromodulin genes are not disclosed; therefore, promoters of any and all uromodulin genes lack written description. 5) The specification and art did not teach using the 5' regulatory sequences of the uromodulin, renin, erythropoietin, apolipoprotein E, osteopontin, urinary kallikrein, urinary thrombomodulin,

uropontin, nephrocalcin or aquaporin gene to obtain expression of exogenous protein in the urinary tract of transgenic non-human mammals.

Listing possible 5' regulatory sequences having a possible function is not adequate written description. It is merely a wish to know such sequences. The level of expression obtained using the 5' regulatory sequences claimed may be inadequate to obtain detectable levels of protein in the urine, the promoter may not function as expected in the transgenic and the tissue-specificity within the urinary tract may not be adequate to allow secretion into the urine. Therefore, the specification does not provide adequate written description for 5' regulatory sequences claimed that provide expression of exogenous protein in the urinary tract of transgenic non-human mammals (claims 75-100).

Applicants argue the declaration by Dr. Serguei Soukharev teaches obtaining protein expression in the urine using the uromodulin promoter. Applicants argument is not persuasive because the specification and the art at the time of filing did not teach the uromodulin promoter used to make the construct disclosed in the declaration. Nor did the specification provide an assay to reasonably determine the uromodulin promoter. Nor does the declaration teach how the uromodulin promoter was obtained. Therefore, the declaration does not correlate to the specification as originally filed because it contains information that was not known at the time of filing or disclosed in the specification as originally filed.

Applicants argue the skilled artisan would be able to determine appropriate, functional 3' regulatory sequences without undue experimentation from known genes that encode proteins that

are associated with the urinary tract of mammals. Applicants argument is not persuasive. 1) The specification and the art did not teach an assay to determine the 3' regulatory sequences that have the desired function. 2) While Sympson of record taught using the WAP 3' UTR in a transgenic mouse that secreted exogenous protein in its urine, the claims are not limited to the WAP 3' UTR. 3) The specification discloses using 3' regulatory sequences in claims 80 and 96 claimed (page 42, line 19), but the specification and art did not teach the nucleic acid sequence of the 3' regulatory sequences in claims 80 and 96. 4) The specification and art did not teach using the 3' regulatory sequences of the uromodulin, renin, erythropoietin, apolipoprotein E, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin gene to obtain expression of exogenous protein in the urinary tract of transgenic non-human mammals. Listing possible 3' regulatory sequences having a possible function is not adequate written description. It is merely a wish to know such sequences. The specification does not provide written description for using any 3' regulatory sequence as claimed in the instant invention because the specification does not teach more than one such sequence that provides an adequate level of secretion such that the protein is detected in the urine, functions as expected in transgenics and causes secretion into the urine and not a different area of the urinary tract. Therefore, the specification does not provide adequate written description for using any 3' regulatory sequences in the instant invention (claims 78-83 and 91-96).

The specification does not provide adequate written description for any transgenics that express enzymes in their urine (claims 84, 85, 97 and 98). While the specification teaches a

number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Thus, the specification does not provide adequate written description that the combination of elements described have the desired function, i.e. the transgenics express functional enzyme in their urine or the enzyme alters the phenotype of the transgenic. Applicants argue the amendment overcomes this rejection. Applicants argument is not persuasive because claims 84, 95, 97 and 98 require expressing enzymes in the urine.

2. Claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose genome comprises a transgene comprising a nucleic acid sequence encoding a protein operatively linked to a promoter that causes secretion of the protein into the urine of the transgenic mammal, wherein said protein is expressed and secreted into the urine of said transgenic non-human mammal and a method of producing a protein in the urine of said non-human mammal, does not reasonably provide enablement for using 5' regulatory sequences of the uromodulin, renin, erythropoietin, apolipoprotein E, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin genes to obtain expression or

secretion of exogenous protein in the urine of transgenic non-human mammals, using any 3' regulatory sequences to obtain exogenous protein expression in the urine, or expressing an enzyme in the urine of transgenic non-human mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The art of making transgenic mammals is unpredictable for reasons of record. In summary, it is difficult to isolate ES cells from mammalian species and to determine the parameters required to obtain germline transmission of an exogenous transgene such that a phenotypic alteration in the transgenic mammal is obtained. Furthermore, the parameters required to obtain germline transmission of an exogenous transgene differ between mammalian species. The art at the time the invention was made did not teach horse ES cells or how to make transgenic horses. Therefore, it was unpredictable how to make transgenic horses at the time the invention was made. Applicants argue horses are enabled because of the similarity between mammalian species. Applicants argument is not persuasive. The specification does not teach horse ES cells or how to make transgenic horses. It would have required one of skill in the art undue experimentation to determine how to make a transgenic horse at the time the invention was made. Therefore, the specification does not enable making transgenic horses (claims 87 and 100).

The state of the art at the time of filing was that it was unpredictable whether a promoter will have the desired phenotypic effect in transgenics as established in previous office actions

(Strojek, Houdebine, Wall and Kappel all of record). The art did not teach using 5' regulatory sequences of the uromodulin, renin, erythropoietin, apolipoprotein E, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin genes to provide expression of exogenous protein in the urinary tract of transgenic non-human mammals. Therefore, it was unpredictable whether these 5' regulatory sequences would result in expression of exogenous protein in the urinary tract of transgenic mammals. Applicants argue the specification teaches other 5' regulatory sequences known to be associated with urinary tract tissue (page 20-27) which is adequate disclosure to enable one of skill to identify, isolate and use the 5' regulatory sequences claimed. Applicants argument is not persuasive because it was unpredictable whether the 5' regulatory sequences claimed provide expression of exogenous protein in the urinary tract of transgenic non-human mammals. The specification taken with the art at the time of filing taught the WAP and uroplakin promoters provided expression of protein in the urinary tract of transgenic mice and allowed isolation of the protein from the urine (Lubon, US Patent 5,880,327, March 9, 1999; col. 6, lines 45-52; col. 9, line 19; Sympson, May 1994, J. Cell Biol., Vol. 125, 681-693, WAP 3' untranslated region, page 683, col. 1, first para., para. bridging pages 683 and 684; see also page 28, line 24 of the instant application; Sun, WO 96/39494, Dec. 12, 1996; US Patent 5,824,543, Oct. 20, 1998, both of record, page 8, lines 3-12; page 9, lines 15-36; page 10, line 4; paragraph bridging col. 5 and 6, col. 6, line 55, Example 2, all of record; para. bridging pages 38-39 of the instant application). The specification contemplates using 5' regulatory sequences of the uromodulin (page 21, line 2; page 29, line 16 and 26), renin (page 29, line 3 and 26), erythropoietin (page 22, line 32; page 29, line 26), apolipoprotein E (page 28, line 7; page 29, line 3), osteopontin (page 24, line 10), urinary kallikrein, urinary thrombomodulin (page 23, line 7), uropontin (page 29, line 26), nephrocalcin (page 23, line 25;

page 29, line 26) or aquaporin (page 24, line 24; page 29, line 26) genes to provide expression or secretion of exogenous protein in the urinary tract of transgenic non-human mammals (see also page 42, line 19). Simonet of record (1990, J. Biol. Chem., Vol. 265, pages 10809-10812) taught transgenic mice whose genomes comprise a transgene encoding a protein operatively linked to the apolipoprotein E promoter and obtain expression of the protein in the kidney (p 28, line 3). Simonet does not teach the mice secrete the protein in their urine. Merely stating a 5' regulatory sequence functions in the urinary tract is not adequate to enable using the 5' regulatory sequence to obtain expression in the urinary tract of transgenics because the level of expression may be inadequate to detect protein in the urine, because the promoter may not function as expected in the transgenic and because the tissue-specificity within the urinary tract may not be adequate to allow secretion into the urine. The specification does not provide adequate correlative evidence between the WAP or uroplakin promoter to the 5' regulatory sequence claimed such that the 5' regulatory sequences claimed could be used to obtain equivalent levels of expression, target the same tissue within the urinary tract, or allow the exogenous protein to be secreted into the urine. It would have required one of skill undue experimentation to use the 5' regulatory sequences claimed to obtain secretion of exogenous proteins in the urine of a transgenic non-human mammal. Therefore, the specification does not enable using the 5' regulatory sequences claimed to obtain expression of exogenous protein in the urinary tract of transgenic non-human mammals.

The specification taken with the art at the time of filing taught the WAP 3' UTR and using the WAP 3' UTR to obtain expression of protein in the urinary tract of transgenic mice and

allowed isolation of the protein from the urine (Sympson of record, May 1994, J. Cell Biol., Vol. 125, 681-693, WAP 3' untranslated region, page 683, col. 1, first para., para. bridging pages 683 and 684; para. bridging pages 38-39 of the instant application). The art at the time the invention was made did not teach other 3' regulatory sequences, specifically of the uromodulin, renin, erythropoietin, apolipoprotein E, osteopontin, urinary kallikrein, urinary thrombomodulin, uropontin, nephrocalcin or aquaporin genes or using these 3' regulatory sequences to allow secretion of exogenous protein in the urinary tract of transgenic non-human mammals. Therefore, it was unpredictable how to use any 3' regulatory sequences to obtain secretion of exogenous protein in the urinary tract of transgenic mammals. While the specification contemplates using 3' regulatory sequences claimed (page 42, line 19), merely listing possible 3' regulatory sequence is not adequate to enable using such sequence to obtain secretion of exogenous protein in the urinary tract of transgenics. The specification does not teach such sequences or provide an assay to determine such sequences. Furthermore, the level of secretion obtained using such sequences may be inadequate to detect protein in the urine and the sequences may not function as expected in the transgenic. The specification does not provide adequate correlative evidence between the WAP 3' UTR to other 3' regulatory sequences such that other 3' regulatory sequences claimed could be used to allow the exogenous protein to be secreted into the urine. It would have required one of skill undue experimentation to use any 3' regulatory sequence to obtain secretion of exogenous proteins in the urine of a transgenic non-human mammal other than the WAP 3' UTR. Therefore, the specification does not enable using any 3'

regulatory sequence as broadly claimed to obtain secretion of exogenous protein in the urinary tract of transgenic non-human mammals (claims 78-83 and 91-96).

Applicants argue 3' regulatory sequence are required to provide secretion of protein into the urine. However, Sun of record taught obtaining secretion in the urine using the uroplakin promoter in the absence of a 3' regulatory region that was specific to the urinary tract. Therefore, clarification is required. It is noted that the independent claims require secretion of protein into the urine but do not require 3' regulatory sequences. If the 3' regulatory sequence is required to obtain secretion into the urine, it should be incorporated into the independent claims.

The disclosed purpose of expressing enzymes in the urine of animals is to degrade/detoxify feces, urine, microbes or chemical pollutants. Sympson of record taught expressing stromelysin-1 (which degrades collagen) in transgenic mice and D'Armiento of record taught that transgenic mice expressing MMP (which also degrades collagen) do not survive (page 5734, col. 2, line 6). While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Given the purpose of the specification taken with the teachings in the specification and in the art, the specification does not enable expressing enzymes in the urine of a transgenic non-human animal. Applicants argue

the amendment overcomes this rejection. Applicants argument is not persuasive because claims 84, 95, 97 and 98 require expressing enzymes in the urine.

3. Claims 6, 11, 45, 56, 69, 70, 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75 and 88 are indefinite because the phrase "5' regulatory sequences selected from a group consisting of an uromodulin gene..." is unclear. The species listed in the Markush group are genes and not 5' regulatory sequences. Therefore, the species listed in the Markush group are not part of the genus of "5' regulatory sequences". Clarification is required.

Claims 80, 83, 93 and 96 are indefinite because the phrase "3' regulatory sequences selected from a group consisting of an uromodulin gene..." is unclear. The species listed in the Markush group are genes and not 3' regulatory sequences. Therefore, the species listed in the Markush group are not part of the genus of "3' regulatory sequences". Clarification is required.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER